UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,746	09/29/2006	Ingmar Hoerr	22122-00006-US1	9342

23416 7590 05/12/2010
CONNOLLY BOVE LODGE & HUTZ, LLP
P O BOX 2207
WILMINGTON, DE 19899

EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
05/12/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,746	HOERR ET AL.	
	Examiner	Art Unit	
	MARIA B. MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/9/10*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/9/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 2/9/10. Claims 1-17 and 21 are pending

Response to Amendment

Applicants' amendment has been sufficient to overcome the objections to the Specification and oath. Applicants' submission of a translation of the parent documents is sufficient to overcome the rejection under 35 USC 102 as anticipated by Hoerr et al.

Information Disclosure Statement

An IDS filed 2/9/10 has been identified in the application. The signed and considered 1449 forms accompany this action. Documents listed on the IDS as International Search Reports have been considered but have been crossed out as PCT reports do not constitute documents under 367 CFR 1.98.

Claim Objections

Claims 1-17 are objected to because of the following informalities:

These are new objections necessitated by applicants' amendment.

Claim 1 is drawn to a method for immunostimulation in a mammal in need of immunostimulation "whereby an immune response in the mammal is intensified or modulated". It is not clear how the preamble and conclusory steps are related i.e. if the steps that intensify or modulate an immune response are responsible for the method of immunostimulation. In other

words, if there is already an immune response and it is intensified in a mammal then something other then the steps lead to the immunostimulation but the claims do not recite what these are.

Claim 7 should be amended to include the article "a" prior to polycationic and thereafter claim 21 should use a "the".

These are new objections.

Claim 1 recites that the mRNA contains a region that encodes at least one antigen. According to the specification, this is intended to mean that the molecule encoding the antigen is mRNA and not some other molecule accompanying the RNA that is administered. To clarify this relationship, it would be clearer to recite, --at least one mRNA which codes for--, use of "contains" is open and does not limit the claim to only this coding region.

Claim 5 for simplicity should be amended to recite --wherein the mRNA which codes for at least antigen-- as the claim already states that the mRNA contains the coding region.

This objection is maintained for reasons of record in the office action mailed 8/11/09 and restated below.

Claims 1 and 2 have amended presentation of a. and b. to (a) and (b) except in line 1 of claim 2. It would be remedial for consistency to amend this occurrence. Claim 5 recites in the alternative "matrix M1 protein or influenza B matrix". It is improper in this claim as the Markush group language establishes a group wherein the proteins are not listed in the alternative. It would be remedial to omit the language "in particular" and "or" and include these two proteins within the listing. Similar amendment to claim 6 is required.

Claim 4 refer to the method of claim 1 and therefore it is improper to use the article "a"

when referring to the method of claim 1. The article "a" or "an" refer to newly recited limitations.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 5 and 10-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These rejections are maintained for reasons of record in the office action mailed 8/11/09 and restated below.**

Regarding claim 5, the phrase "for example" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

It appears as if by the recitation that the mRNA is in the form of naked or complexed mRNA or in the form of globin UTR-stabilized mRNA is meant the mRNA is naked mRNA, complexed mRNA or globin UTR stabilized mRNA. To be in a form does not reflect that it is actually i.e. UTR stabilized mRNA. **Applicants have not corrected claim 8 and 9.**

Claim 10-15 recites the limitation "the modified mRNA" and/or "the wild-type RNA" in claim 1. There is insufficient antecedent basis for this limitation in the claim. For purposes of art, these claims will be considered to be dependent on claim 9

Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are what the connection between the treatment and the immunostimulation are. It appears as if --wherein the mammal in need of immunostimulation comprises one of the following disorders-- --for which the immunostimulation is carried out in connection with a treatment for the disorders thereof--.

These are new rejections necessitated by applicants' amendment.

Claim 6 recites the limitation "the at least one mRNA encoding a cytokine" in claim 1. There is insufficient antecedent basis for this limitation in the claim. There is not at lest one cytokine in claim1. Rather, claim 1 recites "a cytokine mRNA".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-9 and 12-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Terman et al (US 20050112141; see entire document) in view of Horton et al (US patent 7,268,120; see entire document) and Cannon and Weissman (DNA and Cell biology, 2002, pages 953-961; see entire document). **This is a new rejection necessitated by applicants' amendment.**

Applicants claim a method for immunostimulation in a mammal by administration of at least one mRNA encoding at least one antigen of a tumor in combination with i.e. a cytokine wherein the cytokine if not coadminstered with the RNA.

Terman et al as a whole provide teachings that demonstrate use of tumor antigen nucleic acid (i.e. mRNA, see e.g. table 1 and IV and example 34 and 35 especially ¶ 1258) with either cytokine or CpG or adjuvant RNA to enhance the immune response. For example, use of cytokine as an ISS is taught. "In the present invention, the ISS is inserted into nucleic acid sequences of SAgs and tumor associated antigens which are used to transfect tumor cells, antigen presenting cells, accessory cells including muscle cells in vitro or in vivo by methods given in Example 1-3, 15, 16, 18-23". ISS encompasses a number of cytokines (see e.g. ¶ 164-165). In another example, a string of bead of tumor antigens are prepared and introduced into Sag transfected cells or tumor cells and then treated with Dendritic cells. Terman et al teach that these cells are also activated by cytokine treatment (see e.g. ¶ 0049, 0053) and that CpG DNA is also introduced into the cell (see e.g. ¶ 0675). Furthermore, Sag nucleic acid addition can be considered an adjuvant RNA (nucleic acid is defined as DNA or RNA by Terman et al). For example (See ¶ 0376) "One approach to overcome the possible drawbacks of unfractionated tumor antigens is to use mRNA from tumor cells as a "source" of antigen. mRNA can be amplified from a very small number of cells, permitting the generation of sufficient amounts of antigen from minute amounts of tumor tissue Moreover, tumor-specific mRNA can be enriched by subtractive hybridization to remove RNA that is common to normal tissue. This increases the levels of the relevant tumor-specific antigen(s) that can be achieved, and hence, the potency of the vaccine. More importantly, this approach reduces the concentration of nonspecific antigens

or, possibly, self-antigens, thereby lessening the potential for autoimmunity. Pulsing DCs with RNA is known to be effective in empowering them to induce CTL responses and tumor immunity." Administration of cytokines appears to follow 1 minute to 40 hours post nucleic acid administration, (¶0392), Alternatively, they may be used to initiate adoptive T cell therapy by priming regional lymph nodes T cells which are harvested, expanded in vitro by stimulation with S/D/t cells, accompanied by, or followed with IL-2. The tumor antigen-sensitized T cells are reinfused into subjects as described in Example 29.Rnasin is used (see e.g. ¶ 1254). The compositions are administered naked or complexed (see e.g. ¶ 0940-0942). When preparing the mRNA, use of stabilized sequences such as globin is taught as well as used of analogues (see e.g. ¶ 492, 1249 and 1254). The length of the 5'UTR is minimized and furthermore, polyA sequences are found at the 3' end. Efforts are made to stabilize the mRNA i.e. addition of globin UTR and polyA form SV40 as well as mm-LDL use (see e.g. ¶ 0047 and 0441). It appears absent evidence to the contrary that destabilizing elements are not found in the sequences given these directives. As well, attachment of a ribosome binding site is taught (see e.g. ¶ 0074)

Terman et al do not teach that the antigen mRNA is administered followed by administration of cytokine mRNA.

However, Terman et al do teach that the antigen mRNA is administered followed by administration of cytokines. Furthermore, the art teaches that cytokine mRNA is administered as a preferential way to treat cancer. For example, Horton et al teach that cytokine gene therapy is preferentially with mRNA.

> In one embodiment, the polynucleotide sequence encoding one or more cytokines is RNA. Most preferably, the RNA is messenger RNA (mRNA). Methods for introducing RNA sequences into mammalian cells is described in U.S. Pat. No. 5,580,859.

In fact, the art teaches combination of mRNA antigen encoding sequence with cytokine mRNA sequences see Cannon and Weismann et al.

> Advantages of DNA vaccines apply to RNA vaccines while many of the problems do not. Antigen encoding mRNAs can be delivered as a mixture to provide multiple pathogen epitopes and they can also be mixed with mRNAs encoding immune system modulating proteins such as cytokines to improve immunogenicity or direct the type of response, as has been done with some DNA vaccine candidates (Leitner *et al.*, Prayaga *et al.*, 1997; Chow *et al.*, 1998). Another method used for improving DNA vaccine candidates, codon optimization to increase the levels of protein produced (Uchijima *et al.*, 1998; Nagata *et al.*, 1999; Deml *et al.*, 2001), can be applied to RNA vaccines. Unlike DNA, RNA cannot be integrated into the host cell's DNA, potentially promoting gene dysregulation and associated downstream effects.

Given these teachings, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use cytokine mRNA in the treatment protocol of Terman et al because Terman et al teach that it is within the ordinary skill of the art to use tumor antigenic mRNA to modulate immune responses followed by cytokine treatment and because Horton et al teach that it is within the ordinary skill of the art to use cytokine mRNA for treatment protocols directed to similar methods as those of Terman et al. In KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found in the prior art," (Id. At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on its precedent that obviousness in part is predicated

on use of particular known techniques that are recognized as part of the ordinary capabilities of one skilled in the art. In the instant case, it is accepted that use of cytokine mRNA is done by known methods in the art. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1-17 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Terman et al (US 20050112141; see entire document) Claims 1-3, 5-9 and 12-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Terman et al (US 20050112141; see entire document) and Cannon and Weissman (DNA and Cell biology, 2002, pages 953-961; see entire document) in view of Horton et al (US patent 7,268,120; see entire document) further in view of Draghia-Akli et al (US 7,316,925; see entire document) or Weiner et al (US 20020123099; see entire document). **This is in part a new rejection necessitated by applicants' amendment.**

Applicants claim a method for immunostimulation in a mammal by administration of at least one mRNA encoding at least one antigen of a tumor in combination with i.e. a cytokine or CpG. The mRNA can be modified by increased GC content or increased AU content in the ribosome binding sequence.

The teachings of Terman et al are described above and are applied as before except the mRNA has not been modified by increased GC content or increased AU content in the ribosome binding sequence. Nor is the cationic or polycationic agent listed as protamine or poly-L-lysine or histones.

Cannon and Weisman actually teach that codon optimization is used with predictability to improve vaccines (see passage above) and that use of protamine is known and recognized to be used with RNA vaccines,

> Hoerr *et al*. compared naked RNA to protamine condensed RNA and discovered that they could obtain specific CTL activity after a single intradermal injection into the ear pinna with 30 *m*g of condensed RNA (Hoerr *et al*., 2000). Liposome conjugated protamine condensed RNA could also provoke a CTL response when injected IV or SC (Hoerr *et al*., 2000).

Draghia-Akli et al teach that a bias of GC content can increase mRNA stability (see e.g. ¶ 0067).

Weiner et al teach that the environment of the ribosome binding site is improved by an AT rich sequence (see e.g. ¶ 0062).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to improve mRNA stability according to the methods of Draghia-Akli and Weiner et al for the methods taught by Terman et al because Terman et al teach that it is within the ordinary skill of the art to use tumor antigens mRNA to modulate immune responses and that stable mRNA is preferred and because Draghia-Akli and Weiner et al teach that it is within the ordinary skill of the art to alter nucleotide content to improve the stability. In KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found in the prior art," (Id. At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on its precedent that obviousness in part is predicated on use of particular known techniques that are recognized as

part of the ordinary capabilities of one skilled in the art. In the instant case, it is accepted that generation of increased stability of mRNA is done by known methods in the art. As well, it is within the ordinary skill of the art to use available methodologies to modify mRNA stability and one would have been motivated to do so in order as the ability do so by applying conventional methodologies. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to arguments

Applicant's arguments have been considered but are not persuasive for the following reasons. Applicants argue that Terman et al do not teach use of mRNA as a source of antigen coding sequences. However, Terman et al specifically teach that mRNA is useful in overcoming obstacles in treatment protocols,

[0376] One approach to overcome the possible drawbacks of unfractionated tumor antigens is to use mRNA from tumor cells as a "source" of antigen. mRNA can be amplified from a very small number of cells, permitting the generation of sufficient amounts of antigen from minute amounts of tumor tissue Moreover, tumor-specific mRNA can be enriched by subtractive hybridization to remove RNA that is common to normal tissue. This increases the levels of the relevant tumor-specific antigen(s) that can be achieved, and hence, the potency of the vaccine. More importantly, this approach reduces the concentration of nonspecific antigens or, possibly, self-antigens, thereby lessening the potential for autoimmunity. Pulsing DCs with RNA is known to be effective in empowering them to induce CTL responses and tumor immunity.

Applicants argue that use of cytokines following mRNA introduction is not taught by Terman et al. However, Terman et al teaches several methods wherein antigenic vaccination is followed by administration *in vivo* of cytokines,

[0049] For example, a host can be vaccinated against a particular cancer by administering tumor cells transfected with nucleic acid encoding a SAg. Alternatively, a SAg transfected cell is used to activate a host T cell population in vitro. This activated T cell population is then administered to a host as a cancer treatment (immunotherapeutic agent). **Once activated ex vivo or in vivo, these T cells are expanded with cytokine treatment such as IL-2 treatment**.

[0845] Tumor associated antigen immunization is also involved in the binding of peptides to MHC class I bearing APCs of multiple origins. **Various cytokines including, but not limited to, IL-1, IL-2, IL-4, IL-12, or LPS are used in vitro or in vivo** to expand the antigen specific clone of T cells and avert the development of T cell anergy.

1141] Effector T or NKT cells harvested by centrifugation at 500.times.g for 15 min and the cell pellets are pooled. After washing the cells in HBSS, the cell are resuspended in 200 ml of normal saline containing 5% human serum albumin and 450,000 IU of IL-2 for transfer. Each recipient will receive four escalating doses or 33 million, 100 million, 330 million and 1 billion cells per square meter of body surface area each given one week apart. Cells are infused through a subclavian central venous catheter over a 30-minute interval. IL-2 administration i.v. **is commenced immediately after completion of cell infusion at a dose and schedule of 180,000 IU/ml every 8 h. for 5 days**. All patients receive indomethacin (50 mg P.O.) every 8 h, acetaminophen (650 mg P.O.) every 6 h. and ranitidine (150 mg P.O.) every 12 h while receiving IL-2 in order to reduce febrile and gastric side effects. As controls, a cohort of patients is treated with the in vivo tumor vaccination step and IL-2 without the tumor effector cells. Patients will be followed for clinical response every 4 weeks for 2 months with repeat radiological examinations.

Hence, Terman et al does embrace mRNA encoding antigen introduced *in vivo* followed by cytokine administration wherein this administration is separately introduced.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Maria B Marvich, PhD
Primary Examiner
Art Unit 1633

/Maria B Marvich/
Primary Examiner, Art Unit 1633